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Method development and validation of Ceritinib in bulk and pharmaceutical dosage form by UV spectrophotometry

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ABSTRACT

UV spectrophotometric study is the most economical method for studying and validating the drug. In this present study, a new method has been developed and validated for Ceritinib in its bulk form and its dosage form. Ceritinib showed the maximum absorbance at 206nm. The method obeyed Beer Lambert's law and the linearity concentration range was found to be 2-10 µg/ml. The results for other validation parameters were analyzed statistically and were found to fall within the acceptance criteria. The recovery studies and assay studies were found to be satisfactory.

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INTRODUCTION

IUPAC name of Ceritinib is 5-chloro-2-N-(5-methyl-4-piperidine-4-yl-2-propan-2-yloxyphenyl)4-N-(2-propan-2-ylsulfonylphenyl)pyrimidine-2,4-diamine. Molecular formula of Ceritinib is $C_{28}H_{36}ClN_5O_3S$ and it has molecular weight of 558.138 g/mol. It is a solid crystalline substance which has a solubility in different organic solvents like DMSO, ethanol and DMF (dimethylformamide) with solubility value is respectively 16, 1 and 12 mg/ml. Ceritinib inhibits Anaplastic lymphoma receptor or CD246 (cluster of differentiation 246), which is an enzyme that in humans is encoded by the ALK gene. About 45% of NSCLCs have a chromosomal rearrangement that generates a fusion gene between EML4 (echinoderm microtubule-associated protein-like 4) and ALK (anaplastic lymphoma kinase), which results in constitutive kinase activity that kinase (ALK) also known as ALK tyrosine kinase

contributes to carcinogenesis and seems to drive the malignant phenotype. Metabolism of Ceritinib takes place primarily in hepatic cells by the CYP3A4 enzyme. Absorption of Ceritinib was increased with food intake and the greatest impact can be seen when high-fat content is consumed. Since the Ceritinib shows inhibition of CYP3A hence concomitants of other CYP3A substrates, inhibitors, and inducers are not recommended. (Nancy M. Nix et al., 2015). Ceritinib can cause side effects such as bradycardia, vision disorders, gastrointestinal toxicity, and interstitial lung disease neuropathy. The preclinical studies result showed Ceritinib was more potent than Crizotinib. The author also reported that the patients with resistance to one or two ALK inhibitors due to mutations in ALK can still respond to Ceritinib with varying specificity for ALK. The author suggested

regardless of resistance mutations in ALK, in the patients with ALK-rearranged NSCLC Ceritinib was found to be highly active including those patients who had disease progression with crizotinib treatment. A literature survey has indicated that despite clinical importance very few studies has been done on the method development and validation of Ceritinib by UV spectroscopy. Therefore the present study deals with the accurate and precise method for estimation of Ceritinib in the bulk and pharmaceutical dosage form by UV spectrophotometry.

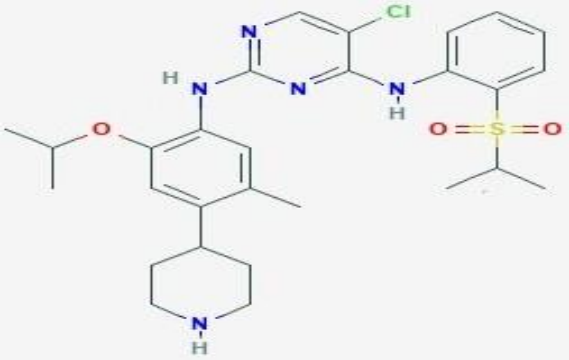

Figure 1: Structure of Ceritinib

Materials

Ceritinib was gifted by AstraZeneca Pvt. Ltd, Bangalore. The commercial tablets of these drugs are available in the Indian market. Other chemicals used were analytical grade and HPLC grade.

Instruments

Shimadzu UV - 1700 UV/VISIBLE spectrophotometer with UV probe 2.10 software and 1 cm matched quartz cells were used for absorbance measurements. Analytical balance used for weighing standard and sample was SHIMADZU AUX 220 Uni Bloc PAT 1987.

Preparation of standard stock solution

The drug Ceritinib has weighed 10mg accurately. This was transferred into the 10ml volumetric flask. The volume was made up to the mark with methanol. The solution was sonicated for 10mins. The concentration of this solution is 1000µg/ml. This solution is considered as a stock solution. From this stock solution, the working solution is prepared by pipetting 1ml and is transferred to 10ml volumetric flask and solution was made up to the mark with methanol. The concentration of this solution is 100µg/ml.

Selection of λmax

From the above solution, a working solution of concentration 100µg/ml was prepared. Different concentration of solution for linearity range was prepared. In this, the mid concentration solution was considered for determining the λmax. This solution was scanned from the range of 200nm400nm which is the ultraviolet range in the electromagnetic spectrum. Methanol is used as blank or reference solution.

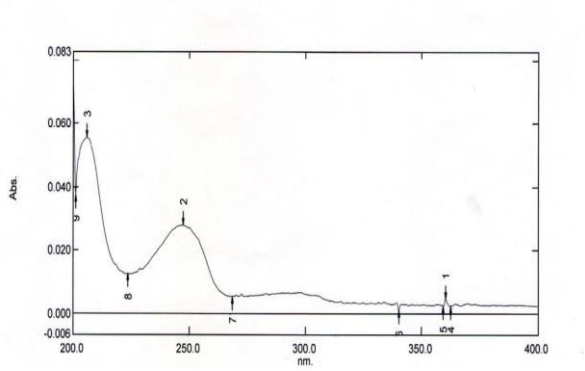

Figure 2: UV spectrum of Ceritinib in the standard solution

Linearity Curve

Linearity curve was prepared for Ceritinib. The standard stock solution 1000µg/ml by weighing 10mg of the drug into 10 ml volumetric flask and the volume was made up to the mark with methanol as diluents. From this working solution of 100µg/ml is prepared by transferring 1ml of the stock solution to 10ml volumetric flask and the volume was made up to the mark with methanol. This becomes a working solution. The linearity range fixed for Ceritinib is from 2–10 µg/ml is prepared by diluting 0.2ml, 0.4ml, 0.6ml, 0.8ml and 1.00ml from the standard working solution to respective 10ml volumetric flask and the volume was made up to the mark by ethanol. These solutions were read at the wavelength which gives maximum absorbance to Ceritinib against methanol as blank. All reading was repeated thrice to get the statistical report. The calibration curve was constructed were x-axis being a concentration of the drug and y-axis being correspondence mean absorbance.

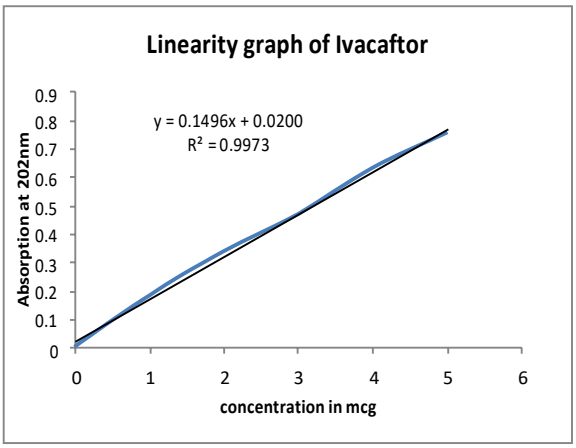

Figure 3: Linearity curve of Ceritinib

Table 5: Study of linearity

Trial I	Absorption at 202 nm	Trial II	Absorption at 202 nm	Trial III	Absorption at 202 nm
2	0.020	2	0.020	2	0.020
4	0.038	4	0.038	4	0.037
6	0.056	6	0.057	6	0.056
8	0.073	8	0.074	8	0.075
10	0.089	10	0.088	10	0.090

LOD and LOQ

LOD and LOQ are calculated from the linear curve of the respective standards based on their linear regression coefficient values. LOD is determined using the formula 3* Sa/b where Sa is the standard deviation of the response and b is the slope value. LOQ is expressed as 10* LOD. Here Sa which is the standard deviation of the response is taken by y-intercepts of the linear regression coefficient.

Table 1: Average Absorption values

Concentration in mcg	Average Absorption at 202nm
2	0.020
4	0.037
6	0.056
8	0.074
10	0.089

Table 2: Limit of detection and Limit of quantification of Ceritinib

Sl. no.	Slope	Intercept
1	0.0089	0.0016
2	0.0089	0.0018
3	0.0091	0.001
Mean	0.008966667	0.001466667
STDEV	0.00011547	0.000416333
LOD	0.139293636	
LOQ	1.392936357	

Table 3: Intraday Precision study of Ceritinib

Sl. no.	Peak absorption at 206nm
1	0.052
2	0.052
3	0.051
4	0.051
5	0.051
6	0.052
Mean	0.051
StDev	0.0005
%RSD	1.063

Accuracy

Accuracy level at 80% for Ceritinib the spiked concentration was 4.8µg/ml, at 100% level the spiked concentration was 6µg/ml and at 120% the spiked concentration was 7.2µg/ml. Percentage of release and found concentration was calculated at every level. At every level the determination was followed thrice to prove statistically.

Table 4: Interday Precision study of Ceritinib

Sl.No	Day-1	Day-2	Day-3
1	0.054	0.05	0.051
2	0.055	0.05	0.051
3	0.054	0.049	0.05
4	0.056	0.05	0.05
5	0.055	0.05	0.05
6	0.055	0.049	0.049
Mean	0.054	0.049	0.050
StDev	0.0007	0.0005	0.0007
%RSD	1.372	1.0397	1.500

Precision

This method was carried out by doing repeatability intraday precision and interday precision using the mid concentration of the linearity range. 6 µg/ml of Ceritinib was analyzed at λ max that is at 206nm repeatedly 6 times. The absorbance obtained at each time is recorded for intraday precision. In Interday the procedure is the same as that of Intraday, but instead of testing the repeatability on the same day here it is tested in the three consecutive days.

Robustness

This method is done to see its efficiency of the drug to remain unaffected when small changes in the optimum condition are done. To determine this small variation s are done in the experimental conditions and is then evaluated. .The changes were done in the wavelength at ±2nm. Moreover, for every change, the absorbance was recorded in triplicates. The changes were done in the concentration at ±0.5µg/ml. Also, for every change, the absorbance was recorded in triplicates.

Assay Value

Amount of drug content present in tablet formulation is calculated. The tablet form of these drugs was procured from the market.

RESULTS AND DISCUSSION

The method developed here for the estimation of Ceritinib in the API form and the dosage form was found to be accurate and precise. The linearity

Table 6: Study of Robustness

Sl.No	Robustness parameter	Mean	Standard deviation	% RSD
1	Concentration			
	5.5µg/ml	0.048	0.0005	1.186
	6µg/ml	0.055	0.001	1.818
	6.5µg/ml	0.057	0.0005	1.001
2	Wavelength			
	202nm	0.050	0.0005	1.139
	206nm	0.053	0.0005	1.082
	208nm	0.053	0	0

Table 7: Study of Accuracy

Level of recovery	Spiked in mcg/ml	Theoretical absorbance	Practical absorbance	% of release	Found in mcg/m
120	7.2	0.059	0.058	99.154	7.139
100	6	0.056	0.056	100.535	6.032
80	4.8	0.039	0.038	99.645	4.782

Table 8: Assay value

Tablet	Label claim	Assay value of tablet	% Recovery
Ceretinib	450mg	441.9mg	98.21%

Table 9: Study of Ruggedness

Analyst 1		Analyst 2	
Sl. no.	Peak absorption at 202nm	Sl. no.	Peak absorption at 202nm
1	0.052	1	0.049
2	0.051	2	0.050
3	0.051	3	0.049
Mean	0.051	Mean	0.049
StdDev	0.0005	StDev	0.0005
%RSD	1.124	%RSD	1.170

Table 10: Summary of Method Development and Validation of Ceritinib

Sl. No	Parameters	Results
1	Beer's law limit µg/ml	2-10 µg/ml
2	Absorption maxima in nm	206nm
3	Standard regression equation	y = 0.0089x + 0.0013
4	Correlation coefficient (r^2)	0.998
5	Accuracy	99%-100%
6	Precision –Intraday % RSD	1.06%
7	LOD	0.13
8	LOQ	1.39
9	Robustness % RSD	Wavelength 1.13,1.08,0 Wavelength 1.18,1.81,1.00
10	Ruggedness % RSD	1.12 and 1.17
11	Assay	98.21%

concentration range fixed here was 210µg/ml which obeyed Beer-Lambert's law. The m ethod also proved to be effective for the recovery studies which were very close to 100%. The method is stable and its very clear that there is no interference of the excipients. The minor variation did in the parameters of wavelengths and concentrations in the robustness study did not show any deviations in the reading and the % RSD was within the limit not exceeding 2. Therefore this method is quite efficient which can be adapted for the routine quality control procedures for the bulk drug and as well as for the formulated dosage forms of Ceritinib.

CONCLUSION

The developed new method for UV spectroscopic studies of Ceritinib is fast, easy, highly reproducible, efficient, accurate and inexpensive study. The present method was validated according to the ICH guidelines. As the results were within the acceptance criteria, it is found to

be satisfactory and hence can be used in the routine analysis of Ceritinib in the bulk form and the dosage forms.

REFERENCES

Makoto Nishio, Haruyasu Murakami, Atsushi Horiike, Toshiaki Takahashi, Fumihiko Hirai, Naoko Suenaga, Takeshi Tajima, Kota Tokushige, Masami Ishii, Anthony Boral,

Matthew Robson, Takashi Seto. Phase I Study of Ceritinib (LDK378) in Japanese Patients with Advanced, Anaplastic Lymphoma Kinase-Rearranged Non–Small-Cell Lung Cancer or Other Tumors. J Thorac Oncol. 2015;10:1058–1066.

Alice T. Shaw, Dong-Wan Kim, Ranee Mehra, Daniel S.W. Tan, Enriqueta Felip Laura Q.M. Chow, D. Ross Camidge, Johan Vansteenkiste, Sunil Sharma, Tommaso De Pas, Gregory J. Riely, Benjamin J. Solomon, Juergen Wolf, Michael Thomas, Martin Schuler, Geoffrey Liu, Armando Santoro, Yvonne Y. Lau, Meredith Goldwasser, Sc.D., Anthony L. Boral, Jeffrey A. Engelman. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. N Engl J Med. 2014 March 27;370(13):1189–1197:doi:10.1056/ NEJMoa 1311107.

ICH harmonised tripartite guideline. Validation of analytical procedure, test and methodology, Q2(R1). 2005.